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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,650	02/09/2004	Doug Hui Huang	034827-1502	3526

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EXAMINER	
KIM, YOUNG J	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/775,650	HUANG ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on January 5, 2007.

Preliminary Remark

Claims 1-23 are canceled.

Claim 28 is new.

Claims 24-28 are pending and are under prosecution herein.

Priority

The parent application 10/659,582 to which instant application claim priority under 35 U.S.C. 120, contains proper written support for SEQ ID Numbers 13 and 14 (examined invention), and thus priority is accorded.

The effective filing date of the present application is September 9, 2003 therefore.

Claim Objections

The objection to claim 24 for not being drawn to the elected invention, made in the Office Action mailed on September 6, 2006 is withdrawn in view of the Amendment received on January 5, 2007.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claim 24-26 under 35 U.S.C. 103(a) as being unpatentable over Wall et al. (Human Mutations, 1995, vol. 5, pages 333-338; IDS reference) in view of Shuber et al. (U.S. Patent No. 6,818,404, issued November 16, 2004, filed April 11, 2002, priority October 23, 1997; IDS reference), made in the Office Action mailed on September 6, 2006 is maintained for the reasons already of record.

In addition, the rejection of new claim 28 is included herein, as being ***necessitated by Amendment*** (by way of its addition).

Applicants' arguments presented in the Amendment received on January 5, 2007 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Wall et al. disclose a method of amplifying know mutations on known cystic fibrosis gene, and in particular, 31 mutations found on exons 3, 4, 5, 7, 9, 10, 11, 12, 13A, 17B, 19, 14B, 21, and intron 19 (page 333, 2nd column, 1st paragraph; Table 1) via use of primer sequences flanking the desired mutations.

It is noted that SEQ ID Numbers 13 and 14 flank the mutation, N1303K (see instant specification page 33) found on exon 21. This exact mutation is detected by Wall et al. (Table 1).

Wall et al. employ primers flanking the mutations R117H, 621+1, and Y122X were found on exon 4. These exact mutations are flanked by the primer of SEQ ID Numbers 3 and 4 (see instant specification page 19 and 20).

Wall et al. employ primers flanking mutation 3846+10 kb found on intron 19 (Table 1, page 335). This exact mutation is flanked by the primer of SEQ ID Numbers 5 and 6 (see instant specification page 32, top).

Wall et al. employ primers flanking mutations R334W, R347P, and R347H on exon 7 (Table 1, page 335). These exact mutations are flanked by the primer of SEQ ID Numbers 7 and 8 (see instant specification pages 21 and 22).

Wall et al. employ primers flanking mutation 1898+1 for exon 12. This mutation is flanked by the primer of SEQ ID Numbers 9 and 10 (see instant specification page 27).

Wall et al. employ primers flanking mutation 2789+5 on exon 14b (Table 1). This mutation is flanked by the primer of SEQ ID Numbers 11 and 12 (see instant specification page 29).

Wall et al. employ primers flanking mutations G551D, G542X, S549R(T-G), 1717-1, R560T, R553X, S549N on exon 11 (Table 1). These mutations are flanked by the primer of SEQ ID Numbers 15 and 16 (see instant specification pages 24 and 25).

Wall et al. employ primers flanking mutations W1282X and 3905insT on exon 20 (Table 1). These mutations are flanked by the primer of SEQ ID Numbers 17 and 18 (see instant specification page 32).

Wall et al. employ primers flanking mutation G85E on exon 3 (Table 1). This mutation is flanked by the primer of SEQ ID Numbers 19 and 20 (see instant specification page 18).

Wall et al. employ primers flanking mutation A455E on exon 9 (Table 1). This mutation is flanked by the primer of SEQ ID Numbers 21 and 22 (see instant specification page 23).

Wall et al. employ primers flanking mutation 2184delA on exon 13 (Table 1). This mutation is flanked by the primer of SEQ ID Numbers 23 and 24 (see instant specification page 28).

Wall et al. employ primers flanking mutations ΔF508, ΔI507, Q493X, and V520F on exon 10 (Table 1). These mutations are flanked by the primer of SEQ ID Numbers 27 and 28 (see instant specification page 24).

Wall et al. employ primers flanking mutations R1162X, 3659delC, and 3849+4(A-G) on exon 19 (Table 1). These mutations are flanked by the primer of SEQ ID Numbers 29 and 30 (see instant specification page 31).

Wall et al. employ primers flanking mutation 711+1 on exon 5 (Table 1). This mutation is flanked by the primer of SEQ ID Numbers 31 and 32 (see instant specification page 21).

In sum, Wall et al. disclose a primer set comprising 14 pairs of primers which flank the above discussed mutations.

Wall et al. do no employ the universal primer sequence (GCGGTCCCAAAAGGGTCAGT) appended at the end of the primer sequences which are specific for the nucleic acid sequence flanking the mutations found on CTFR gene.

Shuber et al. disclose a method of amplifying a known region employing the universal sequence (described above) appended at the end of the primers (column 7, lines 57-61).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Wall et al., and Shuber et al. thereby arriving at the invention as claimed for the following reasons.

Wall et al. disclose a well-known method of assaying for mutations found on a gene implicated with a particular phenotype, in the present case, cystic fibrosis. The artisans, in particular devise a plurality of primer pairs which flank a plurality of mutations found across a plurality of exons and intron found on CTFR gene.

Hence, given the fact that the entire sequence of the CTFR gene was known and available to one of ordinary skill in the art at the time the invention was made, coupled with the motivation to assay for mutations found on all exons/intron of this gene (as provided for by Wall et al.) which may implicate an individual with cystic fibrosis, the mutations of which are flanked by the primers of

the instant claims, one of ordinary skill in the art at the time the invention was made would have been motivated to employ any primer pairs which flank the known and disclosed mutations of Wall et al. so as to amplify and detect the presence or absence of mutation in a clinical/research samples. In other words, given that the gene is known and the mutation is known, it would be well within the purview of an ordinarily skilled artisan to design any primer pairs which surround the known mutations.

In addition, one of ordinary skill in the art at the time the invention was made would have been also motivated to append the universal priming sequence of Shuber et al. to the ends of the primer for the benefit of increasing the specificity of the amplification of the target nucleic acids in the sample.

Shuber et al. achieve this benefit by conducting an initial amplification of the target nucleic acids with a primer pair, each of which comprising a portion which is complementary to the target nucleic acid, and a portion which is not complementary to target nucleic acid, wherein the latter portion is high in G-C content (column 3, lines 31-46).

Following the first amplification cycle, the subsequent amplification is achieved by second primer pairs which are specific for the latter portions, which requires a higher melting temperatures, providing for more stringent amplification, resulting in lesser background noise in the amplification/detection method (column 3, lines 8-30).

Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to employ the teachings of Wall et al., so as to arrive at a primer pair which flanks know mutations on CTFR gene, wherein said ordinarily skilled artisan would have been motivated to employ the appended, high G-C content, priming sequences to the ends of the primers (as provided

for by Shuber et al.), for the benefit of achieving specific and more stringent amplification of the target sequences with a reasonable expectation of success.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants traverse the rejection.

Applicants state that the claimed invention is directed to a kit for amplifying sequences of the CTFR gene comprising one or more pairs of nucleic acid primers including SEQ ID NO: 13 and 14 and that Wall reference fails to teach the specific primers recited in claim 24 or even refer to a kit.

Initially, if Applicants are contending that a primers of prior art can be patentable simply based on the fact that said primers are packaged in a kit format, this reasoning is severely flawed.

The art is replete with diagnostic kits which comprise primers of requisite purity/concentration and amounts for the conventionality of kits in the analytical arts for the advantages of convenience, cost-effectiveness, matched and/or preweighed components, etc.

So long as there is a motivation to package the primers of prior art together, one of ordinary skill in the art would be plenty motivated to package said primers of the prior art to arrive at a kit.

The point of contention is that Applicants are arguing that the Wall reference (or record) does not teach the exact sequence claimed by the instant claims, and that based on Applicants' position, arriving at primer sequences, even when derived from a known gene, "clearly constitute technical facts in the area of esoteric technology (page 7, 3rd paragraph, Response).

This argument is not found persuasive.

Holding to Applicants' position would find that absent an explicit disclosure of the exact primer sequence, all primers derived from a known gene would be unobvious.

In other words, Applicants' position would allow one to patent primers which were derived from specific portions of a gene, so long as prior art does not disclose those exact sequences, even though the gene is already known. Such practice would result in countless numbers of patents drawn to primers derived from all possible portions of the gene.

In essence, Applicants are contending that primer consisting of 20 nucleotides would not be obvious over a primer having the same 20 nucleotides with the addition of a single nucleotide, totaling to a primer consisting of 21 nucleotides, as the prior art does not disclose a primer of this ***exact*** sequence.

Similarly, a primer consisting of 20 nucleotides derived from a known target' position 20-39, would be separately patentable over another primer consisting of 10 nucleotides derived from said known target's position 41-50.

In addition, what Applicants' have failed to mention in their argument is that the primer positions covered by the instant claims ***flank*** the ***same mutations*** which have been known in the art, ***and that the primer pairs of Wall et al. flank the same said mutation sites as the instantly claimed primers***.

> "It is noted that SEQ ID Numbers 13 and 14 flank the mutation, N1303K (see instant specification page 33) found on exon 21. This exact mutation is detected by Wall et al. (Table 1)." (from page 5 of the Office Action mailed on September 6, 2006)

So, not only was the sequence of the target gene (CTFR) known in the prior art, the very mutation in which the instantly claimed primers flank, was also known and disclosed by Wall et al.

Hence, what Applicants are contending is that any pair of primers which flank a known mutation would be unobvious over each other, *so long as the primers do not have the exact same sequences*.

It is respectfully submitted that such an assumption would severely underestimate the skill level of an ordinarily skilled artisan.

Contrary to the arguments provided for by Applicants, it is submitted that based on a known gene, as well as known mutations, would give plenty of motivation to a one of ordinary skill in the art at the time the invention was made to arrive at a pair of primers which flank said known mutations, involving routine optimization of well-established conditions.

It would appear that Applicants' statement regarding that, "all primer disclosed by Wall [reference] are distinguished from the primers required in the instantly claimed kit" (page 7, 1st paragraph, Response), is conferred by the fact that Applicants are appending universal primer sequences at the end of the primer sequences which are designed to flank the know mutations found on the known CTFR gene.

As already discussed previously, the prior art not only discloses this exact universal priming sequence (see page 7, 1st paragraph, Office Action mailed on September 6, 2006), but ***even***, the actual *motivation to use them in primers*.

To reiterate (from page 8 of said OA):

> Shubet et al. achieve this benefit by conducting an initial amplification of the target nucleic acids with a primer pair, each of which comprising a portion which is complementary to the target nucleic acid, and a portion which is not complementary to target nucleic acid, wherein the latter portion is high in G-C content (column 3, lines 31-46).
>
> Following the first amplification cycle, the subsequent amplification is achieved by second primer pairs which are specific for the latter portions, which requires a higher melting temperatures, providing for more stringent amplification, resulting in lesser background noise in the amplification/detection method (column 3, lines 8-30).

Shuber reference clearly indicates that the use of universal priming sequences appended at the end of primer sequences allow one of ordinary in the art to use more stringent subsequent amplification steps so as to achieve higher specificity, resulting in lesser background noise in the amplification/detection method.

In Shuber et al.'s own words:

> Accordingly, methods of the invention provide heightened specificity and efficiency in an amplification-based screening method that looks for hypermethylated nucleic acid in a heterogeneous sample. According to preferred (from column 4, lines 37-40)

Therefore, the **facts** are that:

a) the prior art discloses all of the mutations from CTFR gene to which the instantly claimed primers flank;

b) the same exact universal priming sequences appended at the end of the instantly claimed primers ***is known in the art in verbatim***; and

c) said art also explicitly discloses that the use of said universal priming sequences results in, "heightened specificity and efficiency in the amplification-based screening method."

Hence, the prior art not only evidences the motivation to amplify the same mutations to which the instantly claimed primers amplify, **but** also to use the ***same*** universal priming sequences appended at the ends of such primers, for the ***explicit*** benefit of heightened sensitivity and efficiency.

Based on such disclosures, it would be presumptuous for one to state that one of ordinary skill in the art would not have been motivated to derive primers which flanks a known mutation on CTFR gene, with appended prior art universal priming sequences.

While Applicants may rely on Want et al. (published 1994) which states that primers of slightly different position can exhibit 100 to 1000 fold differences in amplification sensitivity, this prior art applies to the amplification of bacterial species, such generalize teachings cannot substantiate and apply to the art in general.

If non-obviousness can be established by relying on a non-relevant state of art, it is respectfully mentioned that Buck et al. (BioTechniques, 1999, vol. 27, pages 528-536), invites a plurality of participants to design "optimal" primer sequences based on a known target sequences

(page 529, 1st and 2nd column), and concludes that no single primer was better than the other and that, "*all* of the submitted primers functioned extremely well" (see page 533, 1st column, 2nd paragraph).

Clearly, Buck et al. would justify the position of the Office.

However, the rejection is not solely based on the result of a single publication, but the knowledge of the art as well as the motivation provided in the art to amplify a particular region while employing appended universal primers which results in heightened sensitivity as well as efficiency.

Holding to Applicants' contention, that is, all primers are unobvious over each other absent disclosure of the exact sequence of the primers, would allow others of the discipline to claim the exact priming sequence of instantly claimed primers and appending a different GC-clamp sequence thereto. The end-result would be a "new" primer sequence which is not disclosed by Applicants.

Clearly, such reasoning is flawed.

With regard to Applicants' contention that the specification disclose that the claimed primers are "suitable to be used in combination for amplifying different [CTFR] gene segments in a multiplex format," which is "more complex" than standard PCR assay. (page 8, 3rd paragraph).

It is respectfully submitted that Applicants are now claiming an assay, but a kit.

There is a motivation in the art to provide a kit which comprise primers which flank known mutations on CTRF gene, as already discussed above.

Accordingly, the rejection is proper and maintained for the reasons already of record.

The rejection of claim 27 under 35 U.S.C. 103(a) as being unpatentable over Wall et al. (Human Mutations, 1995, vol. 5, pages 333-338; IDS reference) in view of Shuber et al. (U.S. Patent No. 6,818,404, issued November 16, 2004, filed April 11, 2002, priority October 23, 1997; IDS

reference) as applied to claims 24-26 above, and further in view of Claustres et al. (Human Mutations 2000, vol. 16, pages 143-156), made in the Office Action mailed on September 6, 2006 is maintained for the reasons already of record.

Applicants' arguments presented in the Amendment received on January 5, 2007 have been fully considered but they are not found persuasive for the reasons already set forth above.

As Applicants do not present any new arguments, the present rejection is maintained for the reasons already of record (as provided below, "The Rejection") as well as reasons provided above.

The Rejection:

The teachings of Wall et al. and Shuber et al. have already been discussed above.

Neither Wall et al. nor Shuber et al. disclose a mutation found on exon 16 of CTFR gene.

Claustres et al. disclose a mutation found on exon 16 of CTFR gene, wherein the mutation is D993Y, 3120G->A, and 3120+1G->A (Figure 1 on page 147). These mutations are flanked by the primer of SEQ ID Numbers 25 and 26 (see instant specification page 30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to arrive at a collection of primer pairs which include the mutations disclosed by of Claustres et al., that is, mutations found on exon 16, thereby arriving at the claimed invention for the benefit of arriving at a collection of primer sets which is capable of identifying a collection of mutations found on CTFR gene which may be used for diagnosing cystic fibrosis in an individual.

As the desire to detect mutations associated with cystic fibrosis had been well-established, one of ordinary skill in the art at the time the invention was made would have been naturally led and motivated to arrive at a kit which comprises primer pairs which represent a comprehensive collection of known mutations found on cystic fibrosis with a reasonable expectation of success.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by

applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Primary Examiner
Art Unit 1637
3/13/2007

YOUNG J. KIM
PRIMARY EXAMINER

YJK